



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Fallaux et al.

Serial No.: 10/618,526

Filed: July 11, 2003

For: PACKAGING SYSTEMS FOR
HUMAN RECOMBINANT ADENOVIRUS
TO BE USED IN GENE THERAPY

Confirmation No.: 5055

Examiner: S. Pricbe, Ph.D.

Group Art Unit: 1632

Attorney Docket No.: 2578-3833.9US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number EL995986311US
Date of Deposit with USPS January 30, 2006
Person making Deposit: Timothy Palfreyman

Declaration of Dr. Abraham Bout

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Abraham Bout, Ph.D., declare as follows:

1. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 17 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the captioned application or any patent issued thereon.

2. My name is Abraham Bout. I am an inventor of the present application, USSN 10/618,526 (hereinafter referred to as the '526 application), entitled "Packaging Systems for Human Recombinant Adenovirus to be used in Gene Therapy" and am familiar with its contents and somewhat familiar with its procedural history. In that regard, I am informed that an Office action mailed August 29, 2005 questions the inventorship presently set forth with respect to the '526 application.
3. I am informed and believe, as is more thoroughly explained herein, the inventors named on the '526 application did invent the subject matter of the '526 application.
4. I am informed and believe that the '526 application is a continuation of serial number 10/219,414, filed August 15, 2002, which is a continuation of serial number 10/125,751, filed April 18, 2002, which is a continuation of 09/506,548, filed February 17, 2000, now US Patent 6,602,706 (hereinafter referred to as the '706 patent), which is a divisional of serial number 09/334,765, filed June 16, 1999, now U.S. Patent 6,238,893 (hereinafter referred to as the '893 patent), which is a continuation of serial number 08/793,170, filed March 25, 1997, now U.S. Patent 5,994,128 (hereinafter referred to as the '128 patent), which claims priority from International Patent Application PCT/NL96/00244 (hereinafter referred to as the '244 PCT application), filed June 14, 1996, and published as WO 97/00326 on January 3, 1997, which itself claims priority from European Patent Application EP 95201728.3, filed June 26, 1995, and European Patent Application EP 95201611.1, filed June 15, 1995. The named inventors on these patents, applications, and the '526 application are me, Frits J. Fallaux, Robert C. Hoebe, Alex J. van der Eb and Domenico Valerio.
5. I am informed and believe that US Patent 6,395,519 (hereinafter the '519 patent) named the present five inventors and an additional inventor not named on the present invention, Govert Schouten. I am informed and believe that the inventorship of the '519 patent has been corrected to remove Govert Schouten as an inventor, and that this is a matter of public record in the U.S. Patent & Trademark Office files. Therefore I am informed and believe that the inventors of the '519 patent are identical to the inventors of the '526 application.

6. The records at the U.S. Patent & Trademark Office assist in illustrating the progressive development of the invention of the '526 application and the separate inventions of:
- a. US Patent 6,340,595 (hereinafter referred to as the '595 patent) (assigned to Galapagos Genomics N.V. (hereinafter referred to as "Galapagos") by the assignee of the '526 application, under its former name);
 - b. US Patent 6,413,776 (hereinafter referred to as the '776 patent) (assigned to Galapagos by the assignee of the '526 application, under its former name);
 - c. US Patent 6,878,549 (hereinafter referred to as the '549 patent) (assigned to the assignee under its former name Intogene B.V. which has been updated to Crucell);
 - d. US Patent 6,447,768 (hereinafter referred to as the '768 patent);
 - e. US Patent 6,855,544 (hereinafter referred to as the '544 patent);
 - f. US Patent 6,869,794 (hereinafter referred to as the '794 patent);
 - g. US Patent 6,670,188 (hereinafter referred to as the '188 patent), and applications:
 - h. U.S.S.N. 10/036,949 (hereinafter referred to as the '949 application) (assigned to Galapagos by the assignee of the '526 application, under its former name);
 - i. U.S.S.N. 10/002,750 (hereinafter referred to as the '750 application);
 - j. U.S.S.N. 10/432,105 (hereinafter referred to as the '105 application);
 - k. U.S.S.N. 10/497,832 (hereinafter referred to as the '832 application);
 - l. U.S.S.N. 10/644,256 (hereinafter referred to as the '256 application);
 - m. U.S.S.N. 10/494,140 (hereinafter referred to as the '140 application);
 - n. U.S.S.N. 10/512,589 (hereinafter referred to as the '589 application);
 - o. U.S.S.N. 11/039,767 (hereinafter referred to as the '767 application); and
 - p. U.S.S.N. 11/083,590 (hereinafter referred to as the '590 application);
- (hereinafter collectively referred to as the "Unrelated Patents and Applications"), with reference to the filing dates and names of assignees, as will be explained below.
7. The '128 patent was the first issued U. S. patent from the priority '244 PCT application. The application that developed into the '128 patent was assigned to Intogene from the named inventors of the '526 application, as is recorded at

Reel/Frame 008422/0658 on March 25, 1997. Introgene then changed its name to Crucell Holland BV (hereinafter referred to as Crucell), as is recorded at Reel/Frame 013828/0651 on March 11, 2003.

8. What follows is a brief summary of the filing dates and named inventors of the Unrelated Patents and Applications according to the public records:
 - a. The named inventors of the '595 patent, titled "High throughput screening of gene function using adenoviral libraries for functional genomics applications," are me, Ronald Vogels, Helmuth H. G. van Es, and Govert Schouten. The application that matured into the '595 patent was filed on July 21, 1999 and claimed priority to an application filed June 12, 1998. The subject matter of the '595 patent was invented more than a year after the invention of the subject matter of the '526 application.
 - b. The named inventors of the '776 patent, titled "High throughput screening of gene function using adenoviral libraries for functional genomics applications," are me, Ronald Vogels, Helmuth H. G. van Es, and Govert Schouten. The application that matured into the '776 patent was filed on June 12, 1998. The subject matter of the '776 patent was invented more than a year after the invention of the subject matter of the '526 application.
 - c. The named inventors of the '549 patent, titled "Packaging systems for human recombinant adenovirus to be used in gene therapy," are Ronald Vogels and me. The application that matured into the '549 patent was filed on June 14, 1999 and claims priority from an application filed April 24, 1998.
 - d. The named inventors of the '768 patent, titled "Methods of gene therapy with a DNA sequence encoding NOS," are Anton J. van Zonneveld and Stefan F. F. Verlinden. The application that matured into the '768 patent was filed on December 29, 1999.
 - e. The named inventors of the '544 patent, titled "Recombinant protein production in a human cell," are Guus Hateboer, Karina C. Verhulst, Govert J. Schouten, Alphonsus G. Uytdehaag, and me. The application that matured into the '544

patent was filed on April 14, 2000 and claims priority from a provisional patent application filed April 15, 1999.

- f. The named inventors of the '794 patent, titled "Complementing cell lines," are Ronald Vogels, Menzo Havenga, and Majid Mehtali. The application that matured into the '794 patent was filed on June 4, 2002 and is a divisional of USSN 09/713,678, filed Nov. 15, 2000, now U.S. Patent 6,492,169, which is a continuation-in-part of USSN 09/573,740, filed May 18, 2000, now U.S. Patent 6,913,922, which claims the benefit of U.S. Provisional Application 60/134,764, filed May 18, 1999.
- g. The named inventors of the '188 patent, titled "Packaging systems for human recombinant adenovirus to be used in gene therapy," are Ronald Vogels and me. The application that matured into the '188 patent was filed on April 24, 1998.
- h. The named inventors of the '949 application, titled "High throughput screening of gene function using libraries for functional genomics applications," are me, Ronald Vogels, Helmuth van Es, and Govert Schouten. The application was filed December 21, 2001 and is a continuation-in-part of USSN 09/097,239, filed on June 12, 1998. The subject matter of the '949 application was invented more than a year after the invention of the subject matter of the '526 application.
- i. The named inventors of the '750 application, titled "Complementing cell lines" are Ronald Vogels, Menzo Havenga, and Majid Mehtali. The application was filed November 15, 2001 and is a continuation of USSN 09/713,678, filed November 15, 2000, now U.S. Patent 6,492,169, which is a continuation-in-part of USSN 09/573,740, filed May 18, 2000, now U.S. Patent 6,913,922, which claims the benefit of U.S. Provisional Application 60/134,764, filed May 18, 1999. The '750 application has now matured into US Patent 6,974,695 (hereinafter referred to as the '695 patent).
- j. The named inventors of the '105 application, titled "Adenoviral replicons," are Menzo Havenga and Ronald H. P. Brus. The application was filed on May 20, 2003 and claims priority from PCT International Application No. PCT/NL01/00834, filed on November 19, 2001, which claims the benefit of US

Provisional Application 60/249,965, filed November 20, 2000 and EP 0204097.0, filed November 20, 2000.

- k. The named inventors of the '832 application, titled "Production of viruses, viral isolates and vaccines," are Giuseppe Marzio, Maria G. Pau, Dirk J. E. Opstelten, and Alphonsus G. C. M. Uytdehaag. The application was filed January 10, 2005 and claims priority from PCT International Application No. PCT/NL02/00804, filed on Dec. 9, 2002, published as WO 03/048348 A2 on Jun. 12, 2003, which claims the benefit of PCT/NL01/00892, filed Dec. 7, 2001 and EP02075327.2, filed January 25, 2002.
- l. The named inventors of the '256 application, titled "Efficient production of IgA in recombinant mammalian cells," are David H. A. Jones and me. The application was filed August 20, 2003 and is a continuation-in-part of U.S. patent application Ser. No. 09/549,463, filed April 14, 2000, which application claims the benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application Ser. No. 60/129,452, filed April 15, 1999.
- m. The named inventors of the '140 application, titled "Methods and means for producing proteins with predetermined post-translational modifications" are Dirk Jan E. Opstelten, Johan C. Kapteyn, Petrus C. J. J. Passier, Ronald H. P. Brus, and me. The application was filed April 29, 2004 and is a national entry of PCT International Application No. PCT/NL02/00686, filed on October 29, 2002, published as WO 03/038100, which claims the benefit of PCT/NL01/00792, filed October 29, 2001 and PCT/NL02/00257, filed April 19, 2002.
- n. The named inventors of the '589 application, titled "Means and methods for the production of adenovirus vectors" are Ronald Vogels and me. The application was filed October 25, 2004 and is a national entry of PCT International Application No. PCT/EP03/50125, filed April 24, 2003, published as WO 03/104467, which claims the benefit of PCT/NL02/00280, filed April 25, 2002.
- o. The named inventors of the '767 application, titled "Recombinant production of mixtures of antibodies" are Patrick H. C. van Berkel, Ton Logtenberg, Ronald H. P. Brus, and me. The application was filed January 18, 2005 and is a national

entry of PCT International Application No. PCT/EP03/07690, filed July 15, 2003, published as WO 2004/009618, which claims the benefit of EP 02077953.4, filed July 18, 2002 and PCT/EP03/50201, filed May 27, 2003.

- p. The named inventors of the '590 application, titled "Gene delivery vehicles with cell type specificity for mesenchymal stem cells" are Menzo J. E. Havenga, me, and Ronald Vogels. The application was filed March 18, 2005 and is a continuation of USSN 10/010,645, filed November 13, 2001, now US Patent 6,905,678, which claims the benefit of US Provisional Application No. 60/303,734, filed July 6, 2001.
9. As can be seen, each patent and each patent application has different inventors with different filing dates than that of the '526 application. That is because different people invented the different inventions at different times after the inventions described in the '526 application. Further, reference to the titles and claims of each of the Unrelated Patents and Applications helps to illustrate that each invention is separate from that of the '526 application.
10. In 1995, European patent applications were filed disclosing the invention claimed in the '526 application, namely EP 95201728.3, filed June 26, 1995, and European Patent Application EP 95201611.1, filed June 15, 1995. These applications were followed by the '244 PCT application, filed June 14, 1996. The '526 application is a continuation of the national entry originating from these 1995 and 1996 applications. However, the research did not stop and further separate inventions were made by me and others. The further research is at least partially memorialized in the Unrelated Patents and Applications.
11. Some three years after the initial June 1995 priority filing, *i.e.*, on June 12, 1998, a patent application claiming separate inventions was filed for by different inventors than those of the '526 application. To date, the '595 Patent and the '776 Patent (both assigned to Galapagos) have issued both claiming priority to the June 12, 1998 application. Also, the '949 application claims priority to the June 12, 1998 application and remains pending, although according to "public PAIR", the application has been allowed and the issue fee payment verified. These patents and

application were assigned from Crucell, formerly known as Introgene, to Galapagos. I was one of the inventors and am familiar with the other three named inventors of all three of the patents and applications. The title of the '595 patent, the '776 patent and the '949 application, "High throughput screening of gene function using adenoviral libraries for functional genomics applications," illustrates that these are separate inventions from the '526 application, entitled "Packaging Systems for Human Recombinant Adenovirus to be used in Gene Therapy."

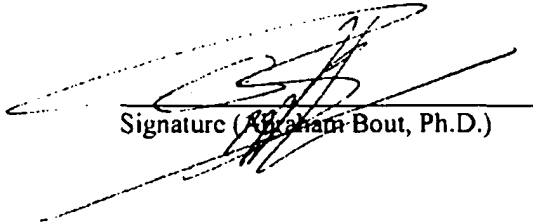
12. On April 24, 1998, an application for a separate invention was filed on by different inventors than those of the '526 application. To date, the '188 patent has issued from that application, and the '549 patent has issued from an application that was a continuation of the application that lead to the '188 patent. I was one of the inventors and am familiar with the other named inventor.
13. On April 15, 1999, an application for a separate invention was filed on by different inventors than those of the '526 application. To date, the '544 patent has issued from that application. I was one of the inventors and am familiar with the other named inventors. The title of the '544 patent, "Recombinant protein production in a human cell," helps illustrate that this is a separate invention from the '526 application, titled "Packaging Systems for Human Recombinant Adenovirus to be used in Gene Therapy."
14. On May 18, 1999, an application for a separate invention was filed on by different inventors than those of the '526 application. To date, the '794 patent has issued from that application. I am familiar with the named inventors and the work they performed. The claims of the '794 patent clearly illustrate that the '794 patent is a separate invention. For example, and not by way of limitation, claim 1 of the '549 patent claims "a packaging cell that complements recombinant adenovirus based on serotypes from subgroup B."
15. On December 29, 1999, an application for a separate invention was filed on by different inventors than those of the '526 application. To date, the '768 patent has issued from that application. The title of the '768 patent, "Methods of gene therapy with a DNA sequence encoding NOS," helps illustrate that this is a separate invention

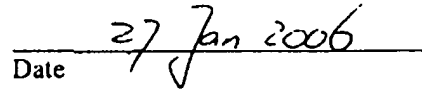
from the '526 application, titled "Packaging Systems for Human Recombinant Adenovirus to be used in Gene Therapy."

16. On December 7, 2001, an application for a separate invention was filed on in the '832 application by different inventors than those of the '526 application. The title of the '832 application, "Production of viruses, viral isolates and vaccines," helps illustrate that this is a separate invention from the '526 application.
17. On August 20, 2003, separate inventions were filed on in the '256 application by different inventors than those of the '526 application. I was one of the inventors and am familiar with the other inventor. The title of the '256 application, "Efficient production of IgA in recombinant mammalian cells," helps illustrate that this is a separate invention from the '526 application.
18. On November 20, 2000, an application claiming a separate invention was filed on in the '105 application by different inventors than those of the '526 application. The title of the '105 application, "Adenoviral replicons," helps illustrate that this is a separate invention from the '526 application.
19. On November 15, 2000, an application claiming a separate invention was filed on in the '750 application by different inventors than those of the '526 application. The '750 application now matured into the '695 patent. I am familiar with the named inventors and the work they performed. The claims of the '695 patent clearly illustrate that the '695 patent is a separate invention. For example, and not by way of limitation, claim 1 of the '695 patent recites "a process comprising: providing a packaging cell that complements recombinant adenovirus based on adenovirus type 35, ..."
20. On October 29, 2001, an application claiming a separate invention was filed on in the '140 application by different inventors than those of the '526 application. I was one of the inventors and am familiar with the other inventors. The title of the '140 application, "Methods and means for producing proteins with predetermined post-translational modifications" helps illustrate that this is a separate invention from the '526 application.

21. On April 25, 2002, an application claiming a separate invention was filed in the '589 application by different inventors than those of the '526 application. I was one of the inventors and am familiar with the other inventor. The claims of the '589 application clearly illustrate that the '589 application is a separate invention. For example, and not by way of limitation, claim 1 of the '589 application claims "A recombinant adenovirus vector comprising structural and non-structural elements of an adenovirus of a first serotype, wherein said recombinant adenovirus vector further comprises a nucleotide sequence encoding a functional E4-orf6, protein or a functional part, derivative and/or analogue thereof, wherein said nucleotide sequence is selected from the group consisting of: E4-orf6-encoding sequence derived from an adenovirus of a second serotype different from said first serotype; E4-orf6-encoding sequence derived from an adenovirus of said first serotype comprising a deletion, mutation, addition and/or substitution in one or more codons of said E4-orf6-encoding sequence; and E4-orf6-encoding sequence comprising a fusion between a part of said E4-orf6-encoding sequence derived from a second serotype different from said first serotype and a part of an said E4-orf6-encoding sequence derived from a third serotype, wherein said third serotype may be identical or different from said first serotype."
22. On July 18, 2002, an application claiming a separate invention was filed in the '767 application by different inventors than those of the '526 application. I was one of the inventors and am familiar with the other inventors. The title of the '767 application, "Recombinant production of mixtures of antibodies" helps illustrate that this is a separate invention from the '526 application.
23. On July 6, 2001, an application claiming a separate invention was filed in the '590 application by different inventors than those of the '526 application. The title of the '590 application, "Gene delivery vehicles with cell type specificity for mesenchymal stem cells" helps illustrate that this is a separate invention from the '526 application.
24. In conclusion, on information and belief, I state that the named inventors of the Unrelated Patent and Applications are correctly named. Further, the inventors of the '526 application have been named correctly.

Serial No. 10/618,526


Signature (Abraham Bout, Ph.D.)


Date